American Association of Tissue Banks

August 23, 2004

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

In Re: ***[Docket No. 2004D-0193]***

Draft "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)"

Dear Madams and Sirs:

The American Association of Tissue Banks [hereinafter referred to as the "AATB" or the "Association"] submits these comments in response to the Food and Drug Administration's (FDA) publication of the above-captioned document. The notice of this draft guidance document appeared in the May 25, 2004 issue of the *Federal Register* [69 *Federal Register* 29835].

The Association understands that the draft guidance document, when finalized, will represent the Agency's current thinking on this topic, and that it has been distributed for comment purposes only. The document provides recommendations for complying with the requirements contained in the donor-eligibility regulations for human cells, tissues, and cellular and tissue-based products (HCT/Ps) (21 CFR part 1271, subpart C) [69 Federal Register 29786]. Those regulations require that an eligibility determination be made for most cell and tissue donors, based on testing and screening for relevant communicable diseases.

I. THE INTEREST OF THE AATB

The AATB is a voluntary, professional, scientific and educational organization. The Association was founded in 1976 and is tax-exempt under Section 501(c)(3) of the Internal Revenue Code.

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The AATB's mission is public health. The Association is dedicated to ensuring that human tissues intended for transplantation are safe and free of infectious disease, of uniform high quality, and available in quantities sufficient to meet national needs.

To further that mission, the Association has, since 1985, published the only standards for tissue banks, the AATB's *Standards for Tissue Banking*. This document is the recognized authoritative source for the industry. Beginning in 1986, the AATB initiated a voluntary Accreditation Program to ensure that tissue-banking activities are being performed in a professional manner in compliance with these *Standards*. All of the AATB's institutional members must be accredited and re-inspected and re-accredited every three years. The Association's membership currently includes nearly 1,100 individual members and 86 accredited tissue banks engaged in the recovery, processing, storage and distribution of human tissue.

The AATB has consistently and publicly supported balanced governmental regulation aimed at safeguarding human tissues from disease transmission. With the publication of the Agency's first regulations in 1993 [62 *Federal Register* 40,429], the AATB publicly supported the FDA's establishment of interim disease transmission requirements for human tissues. The Association has long advocated and continues to support balanced and reasonable FDA regulation of tissue banking.

The AATB's *Standards* contain extensive requirements for donor screening and testing to ensure safety and to avoid disease transmission. With the exception of ocular tissue, AATB-accredited banks provide most of the commonly used structural tissues for clinical use in the United States. The Association is, therefore, extremely interested in the draft guidance document and its potential effects on the safety, effectiveness and supply of human tissue for transplantation.

Over the years, the AATB has provided useful information to assist the FDA in addressing its public health challenges, most notably disease transmission. The Association has worked with the FDA to develop an appropriate regulatory scheme in this evolving field of medicine. These comments are intended to continue that collegial and cooperative spirit. The AATB also intends to continue to provide constructive criticism and recommendations for regulatory changes where it believes they are warranted.

II. COMMENTS

Comment #1

I. INTRODUCTION

A. What is the purpose of this guidance?

Provision. In the fourth paragraph, it states:

> "This guidance does not replace earlier guidance on 21 CFR part 1270 (Ref. 2). This guidance only applies to cells and tissues procured on or after the effective date of the final regulations contained in 21 CFR part 1271, subpart C. [Effective date is May 25, 2005.] "

Recommendations. This section creates a dual regulatory standard. Some donor tissue can be held for an extended period prior to processing, and the shelf life of processed tissue can extend to five years after production. Tissue recovered on or before May 24, 2005 will be regulated under 21 CFR 1270. This will result in dual regulatory requirements for more than 5 years. Practical application of this dual standard may lead to confusion by local FDA inspectors and by the industry.

The AATB suggests that the compliance requirements be clarified in areas where new regulation is less restrictive. For example, under Part 1270, the Summary of Records requires that a listing of testing laboratory names and addresses accompany each tissue. Part 1271 no longer maintains this requirement. AATB proposes, therefore, that the language be changed to reflect that the less restrictive, Part 1271 criteria be applicable for **all** inventory.

Comment #2

II. THE DONOR-ELIGIBILITY DETERMINATION

B. Who makes the donor-eligibility determination?

Provision. In the first paragraph, it states:

> "A 'responsible person' must make the donor-eligibility determination (§ 1271.50(a)). A responsible person is one who is authorized to perform designated functions for which he or she is trained and qualified (§

> 1271.3(t)). You are permitted to make the donor eligibility determination only if you are trained, qualified, and authorized to do so. The donor eligibility determination must be documented (§ 1271.50(a))."

Recommendations. The draft Guidance Document fails to define "trained, qualified, and authorized." In some instances this will be limited to physicians. In other tissue applications, it could allow for physician designees (non-physicians) to make final donor eligibility determinations. Is it the intention of the FDA to accept donor eligibility determinations from non-physicians?

AATB Standard F1.100, Donor Suitability Review, states that:

> "Although the donor's medical, social, and sexual history may be preliminarily screened by technical staff to evaluate acceptability for retrieval or processing, cells and/or tissue shall not be released for transplantation without final review of donor suitability by the Medical Director *or licensed physician designee*." (emphasis added)

The AATB recommends that the FDA incorporate this standard into its Guidance Document and require that the donor-eligibility determination be made by a licensed physician, either the Medical Director or his or her physician designee.

Comment #3

II. THE DONOR-ELIGIBILITY DETERMINATION

C. What is a "relevant communicable disease agent or disease?

Provision. In item number 2 (c), the last part within the listing entitled, "Severe Acute Respiratory Syndrome (SARS)," it states in relevant part:

> "Information about diagnosing and reporting SARS may be obtained at the CDC website at http://www.cdc.gov/ncidod/sars/index.htm or by calling CDC at 888-246-2675...FDA believes it is prudent to recommend donor screening for this illness when CDC lists SARS-affected areas on their website."

Recommendations. There is no guidance offered as to how often review of the referenced website should occur. To maintain compliance continuously would require

constant monitoring of the website. The AATB recommends that the FDA and/or the Centers for Disease Control and Prevention (CDC) alert tissue establishments when the CDC initially reports SARS-affected areas. The AATB will also monitor SARS-affected areas and alert AATB-accredited banks when it is indicated.

Comment #4

II. THE DONOR-ELIGIBILITY DETERMINATION

E. What procedures must I establish and maintain?

Provision. In the third paragraph, it states:

> "Under § 1271.47(d), you must record and justify any departure from a procedure at the time of its occurrence, but you do not have to obtain approval at that time for making the departure. For example, a departure might include the use of a different manufacturer's reagents because the usual manufacturer's reagents were not available at the recovery site. However, before distributing an HCT/P manufactured under a departure from procedure, a responsible person must determine that the departure did not increase the risk of communicable disease transmission."

Recommendations. The AATB suggests adjusting this wording to allow for justifying a departure from procedure when it is discovered (e.g., errors), which can occur later than the time of the occurrence. A departure from a procedure may not be noticed or acknowledged at the time of occurrence. When it is later identified, it can be justified with proper investigation and documentation that demonstrates that the departure did not increase the risk of communicable disease transmission. The discovery of such a departure may take place well after the occurrence, but it can be properly reviewed by a responsible person and justified. The AATB recommends, therefore, that the phrase, "at the time of its occurrence," be deleted.

Comment #5

II. THE DONOR-ELIGIBILITY DETERMINATION

F. What records must accompany the HCT/P after the donor-eligibility determination has been completed?

Provision. "Under § 1271.55 you must provide the following records with each HCT/P: •

- A distinct identification code (such as an alphanumeric code) affixed to the HCT/P container, that relates the HCT/P to the donor and to all records pertaining to the HCT/P and, except in the case of autologous donations or directed reproductive donations, does not include an individual's name, social security number, or medical record number;
- a statement whether, based on the results of screening and testing, the donor is determined to be eligible or ineligible; and
- a summary of the records used to make the donor-eligibility determination."

Recommendations. The guidance identifies the specific documents that must accompany tissue after the donor eligibility determination has been completed. Should this be interpreted to mean that by "completed" this is the point that equates to final donor suitability determination (i.e., after all available documents, including autopsy reports, are reviewed for evidence of risk for communicable disease and the donor is deemed suitable)?

Tissue may be transported under quarantine status to several locations after various stages of eligibility determination have occurred; from a recovery entity that held the tissue while under quarantine then forwards tissue to an affiliated tissue establishment that processes the tissue; from a processor to a storage facility or distributor; from a storage facility to a distributor; from a distributor to an end user (i.e., physician, hospital). Is it FDA's intent that tissues shipped prior to the final suitability review/release for transplant conform to all of these requirements?

Using "eligible or ineligible" in this context is confusing. Perhaps substituting the term 'suitability' for 'eligibility' when referencing HCT/Ps that have completed the final review process and received a final determination may be appropriate. Up to that point, all information used and processes involved would relate to determination of eligibility (as it is used throughout the draft Guidance and associated Rule).

A donor may be considered eligible to donate, and tissue is recovered. Based on new information, the donor and/or the tissue may later be judged as unsuitable. We assume that "completed" should be interpreted to mean that the tissue has been either approved for transplant or judged unacceptable. Eligibility determinations lead to final suitability

determinations. We, therefore, recommend substituting the term "suitable" for "eligible" when referencing HCT/Ps that have completed the final review process and received a final determination.

Comment #6

III. DONOR SCREENING (§ 1271.75)

C. What sources of information do I review?

Provision.

> "When you screen a potential cell or tissue donor, you must review "relevant medical records" for risk factors, clinical evidence, and physical evidence of the relevant communicable diseases listed in section III. A. (§ 1271.75(a)).
>
> "...Relevant medical records means a collection of documents that includes (1) a current donor medical history interview; (2) a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor; (3) other available records (§ 1271.3(s)). We describe these three elements as follows:
>
> > "3. If they are available, the following other records also meet the definition of relevant medical records (§ 1271.3(s)).
> >
> > - "Records or other information received from any source pertaining to risk factors for relevant communicable disease (e.g., social behavior, clinical signs and symptoms of relevant communicable disease, and treatments related to medical conditions suggestive of risk for relevant communicable disease). FDA believes that examples of these records include: medical examiner report, police records, and information from other tissue or medical establishments."

Recommendations. The FDA needs to provide some clarification regarding this provision. Tissue establishments routinely do not pursue police records as "available

information." Questions exist regarding what access tissue establishments may or may not have to police reports even with the consent of the next of kin, who also may be denied access. Authorization to access police reports is not included on donation consent forms. The utility of donation information contained in police reports is uncertain. How strongly will FDA look to tissue establishments to pursue police reports? Should a tissue establishment know of the existence of a police report but not pursue the report, what documented rationale would FDA expect when electing not to pursue the report?

Comment #7

III. DONOR SCREENING (§ 1271.75)

C. What sources of information do I review?

G. What physical evidence do I look for?

Provision. In paragraph C, item number 2, it states:

> "The purpose of the physical assessment of a cadaveric donor or the physical examination of a living donor, is to assess for physical signs of a relevant communicable disease and for signs suggestive of any risk factor for such a disease...Since this is a step in determining donor eligibility, FDA recommends that you establish and maintain standard operating procedures (SOPs) for the conduct of the physical assessment or physical examination (§ 1271.47)."

In paragraph G, it states:

> "Relevant medical records include the report of the physical assessment of a cadaveric donor or the physical examination of a living donor (§1271.3(s)). FDA recommends that you review those records for any of the following signs that may indicate high-risk behavior for or infection with a relevant communicable disease. Some of the following are not physical evidence of HIV, hepatitis, syphilis, or vaccinia but rather are indications of high-risk behavior associated with these diseases. The following are examples of physical evidence to look for:..." (There follows a listing of 14 items.)

Recommendation. The draft Guidance Document lists 14 examples of physical evidence to look for when examining a living donor. To require an exam of a living donor, particularly for physical evidence of sexually transmitted diseases, is intrusive and will reduce donation of cord blood and hematapoietic stem cells. A physical exam this intrusive is not required of blood donors. We recommend that the FDA delete the requirement for physical assessment for volunteer, unpaid living donors.

Comment #8

III. DONOR SCREENING (§ 1271.75)

E. What risk factors do I look for when screening a donor?

Provision.

> "FDA believes that the following conditions and behaviors increase the donor's relevant communicable disease risk. Except as noted in this section, we recommend that you determine to be ineligible any potential donor who exhibits one or more of the following conditions or behaviors.
>
> "9. persons who have had close contact within 12 months preceding donation with another person having clinically active viral hepatitis (e.g., living in the same household, where sharing of kitchen and bathroom facilities occurs regularly) (Ref. 51);"

Recommendations. Current acceptable blood donation risk criteria for "close contact" scenarios involving viral hepatitis are limited to sexual (intimate) contact only (refer to current AABB Standards). Sexual contact screening for donors of HCT/Ps is found in this same section in item number 5 where it states:

> "persons who have had sex in the preceding 12 months with any person described in the previous 4 items of this section or with any person known or suspected to have HIV infection (Refs. 46, 47), clinically active hepatitis B infection (Ref. 38), or hepatitis C infection (Ref. 49)."

In addition, we direct attention to a similar situation described in III, E, item number 20, listing iv, where intimate contact for a xenotransplantation product recipient is well defined and applied to HCT/Ps.

The AATB recommends that the proposed close contact screening criteria cited above for HCT/Ps be removed so that HCT/P donor screening matches that which is recommended in AABB Standards for blood donation. If this is not possible, AATB requests that FDA better define the symptoms for recognizing "clinically active viral hepatitis" (more than that which appears in Section III. Letter F., number 2).

Comment #9

III. DONOR SCREENING (§ 1271.75)

E. What risk factors do I look for when screening a donor?

Provision. In items numbered 18 and 19, deferral is recommended for "persons who have had close contact within the previous 14 days with persons with SARS or suspected SARS (Refs. 33, 45)," and "persons who have traveled to or resided in areas affected by SARS within the previous 14 days (Refs. 33, 45)."

Recommendations. The current CDC recommendations (*MMWR,* December 12, 2003, 52(49); 1202-1206) require a 10-day deferral period (not 14 days) for these SARS scenarios (e.g., close contact, travel, resided in).

The AATB recommends that the above provision be revised to coincide with the CDC's recommendations and to allow for future updates as follows:

18. persons who have had close contact within the previous 10 days or whatever time period the CDC recommends with persons with SARS or suspected SARS (Refs. 33, 45);

19. persons who have traveled to or resided in areas affected by SARS within the previous 10 days or whatever time period the CDC recommends (Refs. 33, 45);

An additional reference number could be added or entirely substituted for the current two that would guide the reader to the proper CDC website (<http://www.cdc.gov/ncidod/sars/index.htm>) and phone number (888-246-2675).

Comment #10

III. DONOR SCREENING (§ 1271.75)
E. What risk factors do I look for when screening a donor?

Provision. In item number 16, deferral is recommended for any potential deceased donors " who have had both a fever and a headache (simultaneously) during the 7 days before donation (Ref. 8)."

Recommendations. This provision requires some clarification. Does the FDA intend that the presence of headache with a fever for any amount of time during the preceding 7 days would result in donor deferral, or is deferral contingent upon the two conditions existing simultaneously for the entire 7 days? This criteria has the potential to exclude appropriate donors unnecessarily (e.g., donors with subarachnoid hemorrhages; motor vehicle accident victims cared for in the hospital for 7 days prior to death, etc.). In absence of other risk factors for West Nile Virus, there must be circumstances when the presence of these two symptoms in a donor history (occurring simultaneously, within 7 days of donation) would be acceptable.

We recommend, therefore, that the guideline for this criteria for evaluating a potential donor be amended, and that it accommodate when no WNV testing will be done as well as when WNV testing could be done.

Comment #11

III. DONOR SCREENING (§ 1271.75)
F. What clinical evidence do I look for when screening a donor?

Provision. In the second paragraph of item number 7, it states:

> "If bacteremia, septicemia, sepsis syndrome, systemic infection or septic shock is specifically noted in the medical records, the donor is ineligible (see Section III. F. 12.)."

Recommendations. The FDA should clarify whether it intends to defer any donor who has the entry of any of the conditions listed above in their medical records, or is the intent to defer donors who have been diagnosed with the condition at the time of death.

Medical records can reference the potential that a patient has shown signs of and/or has been evaluated for bacteremia, septicemia, sepsis syndrome, systemic infection or septic shock. A positive blood culture should be evaluated and should be considered with all other information obtained about the donor, but absent other findings, it is not a reason for deferral. An admission diagnosis of "rule out septicemia," etc., should not automatically cause the donor to be ineligible. There may be information (cultures, blood work, attending physician notations, etc.) that determines the condition has been successfully treated and resolved by the time of death. We recommend, therefore, that the above sentence be revised as follows:

> "If septicemia, sepsis syndrome, systemic infection or septic shock is documented in the medical records as a diagnosis that remains unresolved upon death, the donor is ineligible."

Comment #12

III. DONOR SCREENING (§ 1271.75)

G. What physical evidence do I look for?

Provision. "The following are examples of physical evidence to look for:

> 1. Physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, syphilis, chancroid;"

Recommendations. This provision raises several questions that the FDA should clarify. For example, is it FDA's intention that the presence of herpes simplex (genital, HSV2) is a rule out for HCT/Ps if discovered during a tissue donor physical examination? If the historian reports that there is knowledge of a history of genital herpes, and there is no suspicion that the donor is sexually active outside of a reported monogamous relationship (i.e. marriage), is the donor still considered an unacceptable risk if active genital herpes is noted upon physical exam?

The current estimate of the prevalence of genital herpes is at approximately 45 million adults in the U.S. out of a total population of about 294 million (See http://www.cdc.gov/std/Herpes/STDFact-Herpes.htm and U.S. Census Bureau website). In contrast, HIV positivity is estimated at 1 million people in the U.S. (See http://cdc.gov/mmwr/preview/mmwrhtml/mm5215a1.htm.) Correlation of an active GUD

such as herpes can be associated with a recent co-infection with HIV or viral hepatitis but the entire donor's history should be considered in such a situation.

Comment #13

III. DONOR SCREENING (§ 1271.75)G. What physical evidence do I look for?

Provision. "The following are examples of physical evidence to look for:

14. Corneal scarring consistent with vaccinial keratitis. (Ref. 29)"

Recommendation. This may be particularly difficult to assess on a cadaveric donor. We are unsure if this could be determined with the naked eye, or whether it could only be determined with a microscopic exam. The training photos for vaccinial keratitis available at http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/vac_ker management.html# show that this affliction is difficult to recognize. The website indicates that early stage infection requires slit-lamp examination. The FDA should indicate if this screening is to be done post-recovery and specifically for donated corneas.

Comment #14

III. DONOR SCREENING (§ 1271.75)
G. What physical evidence do I look for?

Provision.

"...The following are examples of physical evidence to look for:

10. Large scab consistent with recent smallpox immunization;
11. Eczema vaccinatum;
12. Generalized vesicular rash (generalized vaccinia);
13. Severely necrotic lesion consistent with vaccinia necrosum; and/or
14. Corneal scarring consistent with vaccinial keratitis. (Ref. 29)"

Recommendation. It is AATB's opinion that FDA should add the following clarification to the above-referenced provision:

"FDA does NOT expect facilities to document the vaccinia risk items at assessment for all donors. FDA would expect facilities to document these risks ONLY for those donors who are determined to be a possible risk due to meeting one of the two criteria (i.e., received the smallpox vaccine or had close contact with someone who has)."

Comment #15

IV. DONOR TESTING: GENERAL (§ 1271.80)

D. If a donor is one month of age or younger, from whom must I collect a specimen?

Provision. If a donor is one month of age or younger, you must collect and test a specimen from the birth mother instead of the donor (§ 1271.80(a)).

Recommendations. This provision raises several questions that the FDA needs to clarify. For example, does the provision in § 1271.80(b), which directs that testing be performed within 7 days before or after donation, also apply to testing a specimen from the birth mother? Also, in the event that the birth mother is unavailable to the recovery agency within the 7-day period before or after donation, are there any circumstances under which a qualified blood specimen from the donor could be used? Utilization of the process as described in "Pediatric Donor (§ 1271.80(d)(2)(ii))" should be a suitable alternative. If using a blood sample from the neonate donor (one month of age or younger) is determined to be an acceptable alternative, why would its use not also be allowed routinely?

AATB Standard D4.351, Specimens, states, "A blood specimen from the natural mother may be substituted for cells and/or tissue donors younger than three months of age." Why did this current draft Guidance only address donors "one month of age or younger" for this specimen collection/testing provision?

In addition, does this provision disallow the donation from an adopted baby? Birth mothers in this instance would likely be unavailable so a blood sample, as well as a risk assessment/history, may be unobtainable. This scenario should be addressed.

Pediatric allograft heart valves from donors in the neonate population remain in high demand and short supply nationwide. Requiring that infectious disease testing be performed on a specimen from the birth mother (only) may devastate the already

reduced availability of one of the few HCT/Ps that can be considered lifesaving (vs. life-enhancing).

Scenarios abound where obtaining a suitable specimen from the birth mother would not be possible, yet the donor's own qualified sample could be used. Provisions should be made to continue to allow infectious disease testing of the neonate donor's blood sample and testing of the birth mother's blood as an acceptable alternative. Since viral antigens and antibodies are known to cross the placenta and can persist in the baby's circulation for up to 3 months after birth (Turgeon, M.L., in Immunology & Serology in Laboratory Medicine, Second Edition, 1996), the one-month time period should be extended to pediatric donors younger than three months of age.

Since there already exists Guidance for obtaining the medical history and assessing behavioral risk by history for the mother of a donor who is 18 months of age or less, and considering that this very young donor population has an overall reduced chance of exposure to viral diseases, there is an increased level of safety which already exists for this donor age group when compared to others. Invariably, the donor's mother or father (or both) is (are) interviewed when completing the risk assessment questionnaire for their child so reliability of the assessment is enhanced when compared to other tissue donor historian scenarios.

A query was performed regarding the applicability of the cited references in the draft Guidance regarding the need to test birth mother's blood only. For cord blood donors, the reasons for using the mother's blood rather than the baby's for infectious disease testing are not directly related to safety concerns for donors of HCT/Ps. The AABB office was contacted to explain the applicable section of their standards for Hematopoietic Progenitor Cell Services, and the NMDP office was contacted to explain their standards regarding cord blood banking. The following reasons were cited:

For using mother's specimen:

1) Operationally, this is obtained prior to cord blood donation so that pre-testing can be performed and unnecessary collection and subsequent liquid nitrogen storage does not occur (reference to "public" cord blood donation scenarios and known viral cross-contamination that can occur from known positive specimens within liquid nitrogen storage freezers);

2) The availability of the mother just prior to or at donation to draw blood for testing is obvious so samples are collected then. If not, and testing occurs much later after storage of the cord blood, there is a greater risk of testing positive over time (increased potential for behavioral risk, exposure risk), and this clouds the risk status afforded to the cord blood at the time of donation; and

3) Access to the mother or the donor at a later date is questionable and unreliable.

For not using cord blood specimen or baby's specimen:

1) Amniotic fluid can contaminate the cord blood specimen which could interfere with infectious disease testing;

2) Manufacturer's test kits are not licensed/labeled for use on cord blood;

3) It is unknown whether viral antigen and antibody is expressed as well in cord blood as is known for whole blood;

4) Testing the baby's blood has not been considered since mother's blood is usually accessible and used for reasons described above; and

5) Testing the mother's blood at or within 7 days before or after the delivery is an adequate alternative to testing the baby's blood, because the mother's blood is the route of exposure for the baby. While testing the baby's blood would also be acceptable, few mothers would consent to cord blood donation if we were required to draw blood from the newborn. Sacrificing a sample of the cord blood unit for serology testing is unacceptable because it decreases the volume of cord blood available to bank, reducing the unit's effectiveness for transplant, and sometimes resulting in an unbankable unit.

The AATB requests that FDA reconsider the restriction posed by this specific provision. We recommend that FDA delete the restriction imposed by this specific Guidance and allow testing to be performed on either the baby's blood or the birth mother's.

Comment #18

IV. DONOR TESTING: GENERAL (§ 1271.80)

F. May I test a specimen from a donor who has undergone transfusion or infusion?

Provision. In item number 4, it states:

> "Pre-Transfusion/Infusion Specimen, We recommend that your SOPs define those elements necessary to determine whether a pre-transfusion/infusion blood specimen is adequate for infectious disease testing, e.g., the amount of hemolysis, storage conditions, and age of the specimen (§ 1271.47(a)). You must perform tests in accordance with the manufacturer's instructions (§ 1271.80(c)), including any instructions concerning factors that may affect specimen acceptability."

Recommendations. The FDA needs to clarify its current thinking regarding what the expected documentation should be when determining whether a blood specimen is adequate for infectious disease testing, e.g., the amount of hemolysis, storage conditions, and age of the specimen. Is each tissue establishment who physically sends the specimens for testing expected to perform this determination/documentation, or is this determination/documentation expected by each entity performing the testing? FDA could also recommend a uniform method of reporting the severity of hemolysis (i.e. none, 1+, 2+, 3+. 4+).

As written, these necessary blood specimen elements that determine their adequacy for infectious disease testing (e.g., the amount of hemolysis, storage conditions, and age of the specimen), are only suggested for suitability of a "Pre-Transfusion/Infusion Specimen". This information should be required to qualify any blood specimen determined to be suitable for testing, whether it was qualified by an algorithm or was obtained before any infusions/transfusions. The Guidance should reflect that these elements must be met for **all** blood specimens used for infectious disease testing. We recommend replacing "Pre-Transfusion/Infusion Specimen" with "Qualified Specimen" in this relevant part.

Comment #16

IV. DONOR TESTING: GENERAL (§ 1271.80)
E. When do I collect a specimen for testing?

Provision.

> "You must collect the donor specimen for testing at the same time as cells or tissue are recovered from the donor, or, if this is not feasible, within seven days before or after the recovery of cells and tissue (§ 1271.80(b))."

Recommendation. The AATB recommends deletion of the phrase, "if this is not feasible." A pre-mortem sample drawn within the defined time limits is preferable due to improved sample quality, and the affects of plasma dilution can be reduced or eliminated by locating a suitable ante-mortem blood sample (less dilute, or undiluted). The current wording can be interpreted as restricting the bank's choice to use the best blood sample available.

Comment #17

IV. DONOR TESTING: GENERAL (§ 1271.80)
F. May I test a specimen from a donor who has undergone transfusion or infusion?

Provision. In item number 1c, it states:

> "The donor received more than 2000 milliliters of any combination of whole blood, red blood cells, colloids, and/or crystalloids within the applicable time frames set out in paragraphs (a) and (b) in section IV.F.1."

Recommendations. The FDA needs to clarify this provision. By citing specific amounts in this Guidance, it appears that FDA is using a general reference to certain amounts administered for all adult donors. However, since the extent of plasma dilution is assessed based on the donor's weight (or age if less than 12 years of age), it is confusing to list specific volumes in this section. Previously, these amounts were referenced to a potential donor who weighed 45-100 Kg.

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IV. DONOR TESTING: GENERAL (§ 1271.80)

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As written, these necessary blood specimen elements that determine their adequacy for infectious disease testing (e.g., the amount of hemolysis, storage conditions, and age of the specimen), are only suggested for suitability of a "Pre-Transfusion/Infusion Specimen". This information should be required to qualify any blood specimen determined to be suitable for testing, whether it was qualified by an algorithm or was obtained before any infusions/transfusions. The Guidance should reflect that these elements must be met for **all** blood specimens used for infectious disease testing. We recommend replacing "Pre-Transfusion/Infusion Specimen" with "Qualified Specimen" in this relevant part.

Comment #19

V. DONOR TESTING: SPECIFIC REQUIREMENTS (§ 1271.85)

A. For what diseases must I test all donors of HCT/Ps, and what tests should I use?

Provision. In item number 3, it states in relevant part:

> "HBV (FDA-licensed screening test for Hepatitis B surface antigen (HBsAg) (Ref. 51) and for total antibody to Hepatitis B core antigen (antiHBc)--(IgG+IgM)) (Ref. 62);
> *Exception for cord blood collection and storage:* When the maternal sample tests negative for HBsAg and reactive for core antibody, cord blood units may be collected and stored in quarantine. Use of these cord blood units, if there is no comparable cord blood unit for the recipient, is not prohibited in cases of urgent medical need (§ 1271.65(b)). If the maternal sample is reactive for HBsAg, you must not collect the cord blood (§ 1271.50(b))."

Recommendation. Some cord blood banks collect the maternal sample at the time of donation. By the time infectious disease testing is completed, the cord blood unit is processed and stored in quarantine. AATB suggests replacing the last sentence with:

> "If the maternal sample is reactive for HBsAg, the cord blood is unsuitable for banking and transplant."

Comment #20

V. DONOR TESTING: SPECIFIC REQUIREMENTS (§ 1271.85)

B. For what additional diseases must I test donors of viable, leukocyte-rich cells or tissue and what tests should I use?

Provision. In item number 1, it states in relevant part that:

> "You must test donors of viable, leukocyte-rich cells or tissue for the following diseases, in addition to those listed in section V.A. (§ 1271.85(b)). You must use an FDA licensed, cleared, or approved test where such a test is available (§ 1271.80(c)).

> "We recommend that you use the tests listed in parentheses:
>
> "b. Cytomegalovirus (FDA-cleared screening test for anti-CMV). Special note on CMV: CMV is not a relevant communicable disease or disease agent. However, establishments are required to test donors of viable, leukocyte-rich cells or tissues for CMV. A donor who tests reactive for CMV is not necessarily ineligible to donate HCT/Ps. You must establish and maintain an SOP governing the release of HCT/Ps from donors whose specimens test reactive for CMV (§ 1271.85(b)(2)). We recommend that the SOPs be based on current information on the potential for disease transmission from the type of HCT/P to be made available for use and that the SOP limit use of an HCT/P based on the CMV reactive status of the recipient."

Recommendation. A positive anti-CMV test result does not indicate whether the donor has active CMV disease or if the donor is capable of transmitting CMV to the recipient. Requiring tissue banks to limit the release of CMV positive HCT/Ps is inappropriate.

For cord blood and hematopoietic stem cells, the transplanting physician should decide whether a unit reactive for anti-CMV is appropriate for his/her patient. Cord blood units listed on NMDP registry are currently tested for anti-CMV with results made available to the transplanting physician. It is unreasonable to transfer the responsibilities of the recipient's attending physician to a tissue-banking establishment.

The AATB recommends that the FDA replace last sentence above with the following:

> "We recommend that the SOPs require notifying the attending physician of the CMV status of the donor. It is the responsibility of the potential recipient's attending physician to determine whether the risk of potential CMV transmission is acceptable."

Comment #21

V. DONOR TESTING: SPECIFIC REQUIREMENTS (§ 1271.85)

B. For what additional diseases must I test donors of viable, leukocyte-rich cells or tissue and what tests should I use?

Provision. Under item number 2, it states:

"FDA believes that examples of viable, leukocyte-rich cells or tissue include, but are not limited to:

- hematopoietic stem/progenitor cells
- semen

"FDA recommends that you consider cells and tissues to be viable and leukocyte-rich based on their status at the time of recovery, even if later processing may remove leukocytes."

Recommendations. The FDA needs to clarify what other classes of HCT/Ps might be considered leukocyte-rich. The AATB currently requires HTLV testing on all tissue donors. If we were to drop this requirement, are there other categories of donors for which we should still require it?

Comment #22

V. DONOR TESTING: SPECIFIC REQUIREMENTS (§ 1271.85)

A. For what diseases must I test all donors of HCT/Ps, and what tests should I use?

Provision. In "Nucleic Acid Testing (NAT)", the last sentence reads:

"FDA does recommend that living donors of HCT/Ps (e.g. hemotopoietic stem/progenitor cell donors, semen donors) be tested with FDA-licensed NAT blood donor screening tests for HIV and HCV".

Recommendations. We recommend that for clarity "embryo and ooctye" should be added to your list of examples.

Comment #23

V. DONOR TESTING: SPECIFIC REQUIREMENTS (§ 1271.85)

A. For what diseases must I test all donors of HCT/Ps, and what tests should I use?

Provision. Under the heading, "Confirmatory tests," it states:

"If you perform a confirmatory test, negative results on a confirmatory test would *not* override a reactive screening test (except for syphilis)."

Recommendation. Recognizing that reproductive donors are living donors and that false positive test results are possible, AATB has current standards that, under specific situations, allow for a donor with an initial reactive test, followed by non-reactive repeat or confirmatory test results, to continue as a donor. We believe that errors by a testing laboratory should be corrected with proper repeat testing and valuable reproductive tissue made available to recipients without jeopardizing the safety of the public.

We recommend that the FDA allow for acceptance of a donor with initially reactive test results followed by non-reactive confirmatory or repeat screening test as follows:

"Reproductive cells and/or tissues from a donor whose blood samples are repeatedly NON-Reactive, using a SCREENING OR CONFIRMATORY assay, for anti-HIV-1, anti-HIV-2, anti-HTLV I and II, Hep B surface antigen, anti-HBc or anti-HBC, following a reactive result, can be used for transplantation if at least two (2) new consecutive blood samples test non-reactive with a minimum of one month between blood collections. Testing must use FDA approved tests and be performed by a laboratory with appropriate local, state or federal accreditation. In such cases the Medical Director or Director must review and approve donor suitability."

Comment #24

VI. ADDITIONAL SCREENING AND TESTING REQUIREMENTS FOR DONORS OF REPRODUCTIVE CELLS AND TISSUES (§§ 1271.75, 1271.80, 1271.85, AND 1271.90)

B. What additional screening must I do for donors of reproductive cells and tissue?

C. What additional testing must I perform on donors of reproductive cells and tissue?

E. Is follow-up testing required for directed donors of semen?

F. Are you required to screen and test a donor of reproductive HCT/Ps for communicable disease agents and diseases if the HCT/Ps were initially collected for use in a sexually intimate partner, but subsequently intended for anonymous or directed donation?

Provision. Sections B and C both address the screening/testing of donors of reproductive cells and tissues who are not sexually intimate partners. Chlamydia and Neisseria gonorrhea are listed under sections B and C as tests required for donation. Oocytes, if retrieved by laparoscopic procedures, are exempted from this testing. Section E states that anonymous semen donors would be required to complete this testing, while directed semen donors would not be required to complete follow-up testing for Chlamydia and Neisseria gonorrhea. Section F discusses the requirements for donation of reproductive tissue that was originally collected for use in sexually intimate partners. The first example listed discusses the requirements for testing of donors (anonymous or directed) of oocytes, semen and embryos cryopreserved by sexually intimate partners. The Guidance Document states that initial screening is required in all cases with follow-up screening required by the semen provider in the case of embryos and anonymously donated semen.

Recommendation. It is our experience that sexually intimate partners who suffer from infertility rarely, if ever, know if they would consider donating their cryopreserved cells or tissue at some time in the future. Their concern is achieving a pregnancy. Prior to their treatment, they have little idea if any of their semen or embryos will be cryopreserved.

FDA's regulations do not require that these individuals be initially tested for any sexually transmitted disease. We strongly believe that the requirement for initial testing will greatly reduce embryo donation. However, we strongly support repeat serology testing (following a six-month quarantine) of all embryo donors, not just the male gamete provider.

In the case of embryo donation, we do not support the requirement of Chlamydia and Neisseria gonorrhea testing after six months. Re-testing embryo donors six months after their IVF procedure, or in most cases years later, would add little, if any, information regarding the safety of the tissue at the time of cryopreservation. Although prior to an IVF procedure the oocyte provider may be tested for these two diseases, our experience indicates that the sperm provider is rarely, if ever, tested because they are sexually intimate partners.

AATB Standard D4.360 (R) states that Chlamydia and Neisseria gonorrhea testing of semen donors shall be repeated at least every six months. The standard further provides that donations collected during intervals in which Chlamydia and Neisseria gonorrhea cannot be ruled out shall be discarded. This assumes repeated donations by

the semen donor over several months. Embryos considered for donation were created by one IVF procedure

We recommend that FDA allow embryo donation with the following provisions:

1. Repeat serology testing is required six or more months after cryopreservation if the donor is available for testing. If a donor is

   not available for repeat serology testing, initial serology testing results would be required.

2. Chlamydia and Neisseria gonorrhea testing is not required initially or later at the time donor qualification.

3. An informed consent is required stating the testing completed and the testing not completed (including Chlamydia and Neisseria gonorrhea). The recipient(s) and the transplanting physician would be required to sign the informed consent.

4. An initial and repeat physical examination of sexually intimate partners, who later become reproductive donors, would not required as stated in 1271.47. However, a comprehensive three-generation family medical/genetic history of each donor is required and must be reviewed and approved by the Medical Director of the cryobank and the transplanting physician.

The Guidance Document recommends that requirements for initial and repeat testing be provided to patients prior to infertility treatment so that they may participate in a donation program later. We do not believe IVF centers will have patient compliance with this procedure when at the same time the FDA is not requiring sexually intimate partners to complete testing prior to infertility treatment. We do not believe that IVF patients know or will have thought about possible donation prior to the IVF procedure. Formal physical examinations of IVF patients are not currently performed. We strongly believe that embryo donation will be severely decreased unless FDA's regulations are modified. We believe that the above recommendations will allow for continued embryo donation and will not increase the risk of transmitting infectious disease.

Comment #25

VI. ADDITIONAL SCREENING AND TESTING REQUIREMENTS FOR DONORS OF REPRODUCTIVE CELLS AND TISSUES (§§ 1271.75, 1271.80, 1271.85, AND 1271.90)

D. What follow-up testing is required for anonymous semen donors?

Provision.

> "At least 6 months after donation, you must collect a new specimen from the donor and repeat all testing required under § 1271.85(a) through (c) (§ 1271.85(d)). You must ***quarantine*** the donated semen until the retesting is complete and the donor is determined to be eligible."

Recommendation. We agree with the requirement for a six-month quarantine of anonymous semen donor specimens and the release of those specimens only after repeat testing to determine donor eligibility. We recommend, however, that FDA allow semen donor banks to test their anonymous semen donors for Chlamydia trachomatis and Neiserria gonorrhea (these tests are not antibody tests) at the time of their last specimen donation, or at any time following that date.

We suggest that the following language be added to the Guidance Document after the first sentence of the above-captioned provision:

> "Chlamydia trachomatis and Neiserria gonorrhea testing may be completed at the time of donation,or at any time following donation, and the test results must be negative before the specimens can be released from quarantine."

Comment #26

VI. ADDITIONAL SCREENING AND TESTING REQUIREMENTS FOR DONORS OF REPRODUCTIVE CELLS AND TISSUES (§§ 1271.75, 1271.80, 1271.85, AND 1271.90)

E. Is follow-up testing required for directed donors of semen?

Provision. "No, we do not require follow-up testing when semen is donated for directed use."

Recommendation. The AATB disagrees with this provision and recommends the following new language:

> "The quarantine requirement for directed semen donors cannot be waived except for valid, documented medical and/or scientific reasons and then only with informed consent of the recipient. A 1271.90(a) donor-eligibility determination is not required."

Comment #27

VII. EXCEPTIONS (§ 1271.85)

A. When is a donor eligibility determination not required? (§ 1271.90)

Provision.

> "There are three situations in which you are not required to make a determination of donor eligibility or to perform donor screening and testing. Special label requirements apply if you do not screen and test...
>
> "If the HCT/Ps are stored for autologous use, then you must label the HCT/Ps 'FOR AUTOLOGOUS USE ONLY.'
>
> "If you do not test and screen a donor, then you must label the HCT/Ps from that donor 'NOT EVALUATED FOR INFECTIOUS SUBSTANCES.' This requirement applies even if you perform some testing and screening, but not all that would otherwise be required for the donor of the same type of cells or tissue...
>
> "If screening or testing indicates the presence of relevant communicable disease agents and/or risk factors for or clinical evidence of relevant communicable disease agents or diseases, you must label the HCT/P with the Biohazard legend shown in § 1271.3(h).
>
> "If reproductive tissue is being donated to a directed recipient under § 1271.90(a)(3), you must label the HCT/P, 'Warning: Advise patient that donor screening and testing were not conducted at the time of donation.'"

Recommendation. Throughout this draft Guidance Document, there are multiple references made to labeling and/or re-labeling containers. In the case of reproductive tissues stored in vials or straws, physical size limitations prohibit labeling containers with phrases such as those listed in 1271.90 (b), "For Autologous Use Only", or "Not Evaluated for Infectious Substances", and/ or biohazard legend symbols. After cryopreservation, re-labeling and/or adding such information is also impossible without irreversibly compromising the specimens. While we agree that this information is important and should be included, we recommend that the Guidance Document provide that, if physical size limitations exist, this information can be disseminated via package inserts or by attachment to an external shipping container.

III. CONCLUSION

The AATB thanks the FDA for the opportunity to comment on the draft guidance document. The Association commends and supports the FDA's efforts to prevent the transmission of communicable disease agents and disease by tissue transplants.

As was said at the outset, the AATB has a long and valued history of working with the Agency to develop an appropriate regulatory scheme in this evolving field of medicine. These comments are intended to continue that collegial and cooperative spirit.

The AATB stands ready and willing to assist the FDA with this draft guidance document in any way that the Agency deems appropriate.

Sincerely,

P. Robert Rigney, Jr., J.D.
Chief Executive Officer

PRRJr/sab